REMARKS

Claims 1, 3-4, 6-7, 19 and 23-27 constitute the claims pending and under consideration prior to this Amendment. Claim 1 has been amended to recite a method for reducing a "T-cell mediated immune response." The amendment is fully supported by the specification. No new matter has been introduced. In particular, support for the amendment to claim 1 can be found, e.g., at paragraph [0034] of the published application (U.S. Publication No. 2005/0118168).

Amendment of claims should in no way be construed as an acquiescence to any of the rejections. The amendments to the claims are being made solely to expedite prosecution of the present application. Applicants reserve the option to further prosecute the same or similar claims in the instant or in a subsequent patent application.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Office Action will be addressed below in the order they appear in the Office Action.

Information Disclosure Statement

Applicants note with appreciation that the Examiner has considered the Information Disclosure Statement filed on December 5, 2008.

Rejections withdrawn – 35 U.S.C. § 102

Applicants note with appreciation that the previous rejection of claims 1, 3, 4, 6, 7, 19, and 23-26 under 35 U.S.C. § 102(b) has been withdrawn.

Claim Rejections – 35 U.S.C. § 112

Claims 1, 3, 4, 6, 7, 19, and 23-27 are rejected under 35 U.S.C. § 112, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse.

First, the Examiner states that although the support for treating an animal "not infected with HIV" is found, the support "is in the context of treating or preventing HIV" (page 4 of the Office Action). Applicants disagree.

Applicants note that the present disclosure teaches at least two distinct inventions: (1) a method for reducing an immune response by inhibiting an interaction between a dendritic cell and a

T cell (in particular by inhibiting an interaction between DC-SIGN and an ICAM receptor), and (2) a method for preventing or treating HIV infection by reducing the adhesion of HIV to the dendritic cells (in particular by reducing an interaction between DC-SIGN and gp120). The first invention is described, for example, at paragraphs [0025]-[0035] of the published application. The specification explicitly states that this is "a first aspect" of the invention (paragraph [0025]), and the method may be used, e.g., to treat autoimmune diseases, to treat allergies, or to induce tolerance (e.g., to prevent transplant rejections) (paragraph [0035]). On the other hand, the second invention, relating to the treatment or prevention of HIV infection, is described, for example, at paragraphs [0070]-[0071] of the published application. The specification notes that this is a "further" aspect of the invention, and an important feature of invention (2) is to inhibit the binding of HIV gp120 to a dendritic cell.

Therefore, invention (1) relates to reducing the interactions between dendritic cells and T cells, whereas invention (2) relates to reducing the adhesion of HIV gp120 molecule to a dendritic cell. These two inventions involve two distinct mechanisms, and target two different patient groups. In particular, Applicants note that when the specification describes the use of an agent to reduce an immune response by blocking the interaction between DC-SIGN and a T-cell (invention (1)), no reference is made to HIV infection. As such, invention (1) is not directed to treating or preventing HIV infection.

Further, it would have been apparent to a skilled person in the art that the claimed methods do not encompass treating an animal with HIV infection. For example, scientific literature published in the field is consistent with the teachings of the present application, concluding that DC-SIGN has two "contrasting" functions. *See, e.g.,* Steinman, *Cell*, vol. 100, 491-494 ("Steinman," submitted as Exhibit B attached to the response dated April 28, 2008), at page 494. Both the present application and Steinmann teach that in a T-cell mediated immune response, DC-SIGN stimulates a resting T cell to promote immunity against an antigen. *See, e.g.*, Steinmann, at page 494. Thus, blocking the interaction between DC-SIGN and a T cell can reduce the immune response to the antigen. Invention (1) is directed to this particular function of DC-SIGN, and is useful for, e.g., treating autoimmune diseases or inducing tolerance. In contrast, in an HIV infection, DC-SIGN facilitates the transmission of HIV to permissive T cells and promotes immunosuppression. *See,*

e.g., Steinmann, at page 494. HIV virus is captured by the binding of HIV gp120 to DC-SIGN. In particular, Applicants note that DC-SIGN-mediated HIV transmission involves a different mechanism as compared to DC-SIGN-mediated T cell response described above. For example, DC-SIGN-mediated HIV transmission does not require that DC-SIGN interact with an ICAM receptor on the surface of a T cell. *See, e.g.*, Steinmann, at page 493. Therefore, a skilled person in the art, in view of the specific teachings of the application and the general knowledge in the art, would have understood that the claimed methods do not encompass treating an HIV infection.

Finally, the fact the application teaches at least two distinct inventions is further highlighted by the Restriction Requirement issued by the USPTO on Feb. 8, 2002 in connection with the corresponding parent application (Application No. 09/719,961, now Patent No. 7,148,329). In particular, Applicants note that Group X of the Restriction Requirement corresponds to the subject matter being claimed in the present application. Group XI of the Restriction Requirement corresponds to the subject matter of treating or preventing HIV invention. In view of this Restriction Requirement, the PTO recognized that invention (1), directed to reducing an immune response by inhibiting an interaction between DC-SIGN and a T-cell, is distinct and independent of invention (2) (relating to reducing the adhesion of HIV gp120 to a dendritic cell).

Second, the Examiner states that the recitation of "an animal in need of" is not sufficient to define a population, and that *Jansen v. Rexall Sundown, Inc* 342 F.3d 1329 (Fed. Cir. 2003) is not analogous to the pending claims. Applicants disagree.

The Examiner states that the term "in need thereof" in *Jansen* is "not analogous" to the present claims because the claims in *Jansen* "recite a condition, anemia, and a cause, a deficiency in folic acid or vitamin B12 in a method of treating a patient in need of." Applicants disagree. The rulings of *Jansen* are not predicated on whether a claim recites a particular disease or condition. Instead, the court in *Jansen* ruled that the preamble "sets forth the objective of the method, and the body of the claim directs that the method be performed on someone 'in need.'" 342 F.3d at 1333. The presently pending claims are similar. Claim 1 recites "the objective" of the method (reducing an immune response) in its preamble, and the body of the claim directs that the method be

performed on someone "in need." *Jansen* does not require that the claims must recite a specific condition or disease. *Jansen* also never indicates that narrowing the objective from "anemia" to "macrocytic-megaloblastic anemia" had any impact on outcome of the ruling. Therefore, since claim 1 clearly states an objective of the method, and the term "in need thereof" directs on whom the method should be performed, the Examiner should give weight to the term "in need thereof" in claim 1.

Nonetheless, solely to expedite prosecution, Applicants have amended claim 1 to specifically recite that the objective of the claimed method is to reduce "a T-cell mediated immune response." This amendment provides guidance to a skilled artisan in determining the patient population, in particular by specifying that the claims are directed to reducing a T-cell mediated immune response only, thus excluding conditions or disorders caused by the innate immune system.

DC-SIGN-T cell mediated immune response is not disease specific. Multiple diseases or conditions can be treated (e.g., preventing rejection of an allograft, allergies, autoimmune diseases). In each case, an undesirable immune response is triggered by an interaction between DC-SIGN and a T cell in a patient. The claimed invention targets such patients by reducing the interaction between DC-SIGN and T cells.

Applicants submit that one of ordinary skill in the art, in view of the teachings of the specification and the general knowledge in the art, would have been able to determine the patient population of the claimed methods without undue experimentation. In particular, the application teaches that DC-SIGN interacts with and activates resting T cells (paragraph [0024]), that reducing dendritic cell-T cell interaction can reduce an immune response (paragraph [0034]), and that reducing an immune response is particularly desirable in inducing tolerance (e.g., preventing transplant rejection), in treating or preventing autoimmune diseases, or in treating or preventing allergies (paragraph [0035]). As such, a skilled artisan would have had no difficulty in determining whether an immune response should be reduced in a patient, and whether the immune response is mediated by the interaction between DC-SIGN and a T cell.

Finally, the Examiner states that claims are not enabled because the specification and additional references submitted by the Applicants "do not show in vivo correlation in the same scope as the claims" (page 5 of the Office Action). Applicants traverse.

First, *in vivo* efficacy data are not required to enable an *in vivo* use. MPEP § 2164.02. In *Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985), the Federal Circuit noted that *in vitro* testing results are generally predictive of *in vivo* testing results:

> In vitro testing, in general, is relatively less complex, less time consuming, and less expensive than in vivo testing. Moreover, in vitro results with respect to the particular pharmacological activity ***are generally predictive of in vivo test results***, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. Iizuka has not urged, and rightly so, that there is an invariable exact correlation between in vitro test results and in vivo test results. Rather, Iizuka's position is that successful in vitro testing for a particular pharmacological activity establishes a significant probability that in vivo testing for this particular pharmacological activity will be successful.
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> ...
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> ... based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and ***therefore a rigorous correlation is not necessary*** where the disclosure of pharmacological activity is reasonable based upon the probative evidence.

Id. at 1050 (emphasis added).

Therefore, actual proof of in *vivo* effectiveness is not required. Scientifically sound explanations, backed by *in vitro* testing, are widely accepted as sufficient evidence to support claims drawn to subject matter commensurate in scope with that support. See, *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995).

The Examiner has the burden to provide reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model (see MPEP 2164.02). This burden has not been met in this case. The Examiner has merely asserted that the level of unpredictability in the art is high and on this basis concludes that one skilled in the art would not associate *in vitro* efficacy with *in vivo* treatment. Nor does the Examiner provide any reasons to doubt that the *in vitro* data correlate with

in vivo efficacy. Accordingly, the Examiner has not met his burden in challenging the enablement of the instant claims.

The Examiner states that "the claims in light of the support found in paragraph 70 is for at risk of HIV infection and the method is to treating or preventing HIV" (page 5 of the Office Action). Applicants traverse for the reasons stated above. In particular, in view of the specific teachings of the specification, a skilled artisan would have understood that the claims are not directed to the treatment of HIV infections.

The instant application sets forth several examples and presents *in vitro* data derived from cell based assays demonstrating that the interaction between dendritic cells and T cells is mediated by an interaction between DC-SIGN on the surface of the dendritic cells and an ICAM receptor on the surface of the T cells. Further, the application demonstrates that an anti-DC-SIGN antibody can inhibit the interaction between DC-SIGN and an ICAM receptor (see e.g., Example 2, paragraph [0100] and Figures 2A and 2C). Example 6 demonstrates that (1) anti-DC-SIGN antibodies prevented the clustering of dendritic cells with ICAM-3-expressing K562 cells (Figure 6B), (2) that anti-DC-SIGN antibodies inhibited the clustering of dendritic cells with PBLs (which include T-cells) (Figure 6C), and (3) most importantly, that anti-DC-SIGN antibodies inhibited the activation of T-cells when T-cells were mixed with dendritic cells (Figure 6D), as discussed in Example 6 and Example 7. These assays are representative of what occurs *in vivo*, i.e., there are interactions between DC-SIGN and T cells which initiates an immune response (see e.g., paragraph [0093] of the instant application). The application also teaches and enables reducing an immune response by inhibiting an interaction between DC-SIGN and a T cell. Therefore, the application teaches and enables reducing a T cell-mediated immune response in an animal in need thereof by inhibiting an interaction between a dendritic cell and a T cell. A person of ordinary skill in the art, without undue experimentation or inventive skills, can make and use the claimed methods based on the *in vitro* data and other disclosure provided by the application.

Finally, Applicants have submitted additional evidence demonstrating that one of skill in the art would expect that the *in vitro* evidence provided in the specification is representative of what occurs *in vivo*. For example, Ingulli, et al., *J. Exp. Med.*, vol 185, 2133-2141 (1997) ("Ingulli,"

submitted as Exhibit A attached to the response dated April 28, 2008) demonstrates that antigen-bearing dendritic cells directly interact with naive antigen-specific T cells (Ingulli, abstract). This result is consistent with *in vitro* experiments suggesting that dendritic cells are initiating APCs for T cell responses (Ingulli, page 2133, left column). Applicants did not cite Ingulli for the purpose of showing an actual change of immune response *in vivo*, as the Examiner mistakenly believed, but to demonstrate that in this area, *in vitro* results are consistent with *in vivo* results. Similarly, Steinman was previously submitted to show that in this area, several *in vivo* studies have corroborated previous *in vitro* results (Steinman, page 492, right column).

Although the specification has not provided *in vivo* data showing an actual reduction of immune response *in vivo*, it is textbook knowledge that T cell activation requires the interaction between dendritic cells and T cells. See, e.g., Janeway et al. (2001), Immunobiology, 5th edition, pages 20-21 ("Janeway," attached herein as Exhibit 1). Janeway teaches that T-cells can be activated by a combination of two signals – an antigen and a dendritic cell. The pending claims are directed to inhibiting the T-cell-dendritic cell interaction, thereby preventing the activation of the T-cell, e.g., a T-cell mediated immune response. In view of the *in vitro* data provided by the present application, and the additional evidence provided by Ingulli and Janeway, one of ordinary skill in the art would have had no reason to question whether the *in vitro* data provided by the application indeed correlate with *in vivo* efficacy.

Furthermore, additional publications in the field indicate that when an anti-DC-SIGN antibody was administered *in vivo*, the antibody successfully bound to DC-SIGN expressed on the surface of dendritic cells *in vivo*. For example, Pereira et al., J. Immunother. 30:705-714 (2007) ("Pereira," attached herein as Exhibit 2) reports the specific targeting of DCs *in vivo* in a nonhuman primate model using antibodies directed against DC-SIGN (see, summary, page 705). As such, Pereira confirms that the *in vitro* data of the present application are reliable and the application correctly predicted the *in vivo* effect. One of ordinary skill in the art would have had no reason to question whether the *in vitro* data provided by the application indeed correlate with *in vivo* efficacy.

In summary, Applicants have shown that an anti-DC-SIGN antibody can inhibit the interaction between dendritic cells and T-cells *in vitro* (by inhibiting the interaction between DC-

SIGN and an ICAM receptor). Various publications in the field have shown that *in vitro* results are consistent with *in vivo* results. Additional studies also demonstrate that *in vivo* administration of anti-DC-SIGN antibody results in the specific targeting of the antibody to DCs *in vivo*. There is no evidence on record indicating a lack of correlation between *in vitro* data and *in vivo* efficacy.

The Examiner has not provided a specific reason to support the conclusion that it would require undue experimentation for a person of ordinary skill in the art to make and use the claimed methods based on the *in vitro* data and other disclosure provided by the application.

Reconsideration and withdrawal of this rejection are respectfully requested.

Related Applications

Applicants wish to bring the Examiner's attention to co-pending, commonly assigned Application Serial No. 11/977,151, filed October 22, 2007. Applicants invite the Examiner to consider previous, on-going, and future prosecution in the co-pending application. Applicants note that the most recent action in the co-pending application is a Response to non-Final Office Action filed on March 13, 2009.

Applicants also wish to bring the Examiner's attention to Application Serial Nos. 10/524,395 (issue fee paid on April 24, 2009) and 10/524,394 (non-Final Office Action mailed on June 2, 2009).

CONCLUSION

In view of the above amendments and remarks, Applicants believe the pending application is in condition for allowance. Early and favorable consideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000.

Applicants believe no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. ALXN-P02-089 from which the undersigned is authorized to draw.

Dated: June 8, 2009

Respectfully submitted,

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